REMARKS

Claims 1-57 are pending in this application, and claims 20-49 are withdrawn from consideration, as directed to non-elected subject matter in response to the November 1, 2005 requirement for restriction. Claims 56 and 57 have been amended to rectify an error in the preambles of these claims. Other claims have been amended to modify typographical errors.

Prior Rejections Withdrawn

Applicants appreciate the indication of the withdrawal of the prior rejections under 35 U.S.C. § 103.

Rejection of Claims 1-19 under 35 U.S.C. § 102

Claims 1-18 and 50-56 are rejected as anticipated by Diaz-Collier *et al.*, EPO publication EP 0 559 632 A1 ("Diaz-Collier"). Applicants respectfully traverse.

The Office alleges the following on pages 2-3 of the instant action:

> Diaz-Collier et al. teach that a ala-TFPI preparation refolded and purified by the method disclosed in Example 1 (page 6+ and esp page 6, para. 2 regarding Ala-TFPI). This TFPI preparation was greater than 95% homogeneous (page 12, line 2), suggesting that there was less than 5% misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts of the TFPI. There is also no evidence or indication that the preparation contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated.

Thus, the Office concludes that the preparation instantly claimed is patentably indistinct from

that of Diaz-Collier, and that the burden has been shifted to Applicant to distinguish Applicants claim from the product of Diaz-Collier.

Applicants reiterate and incorporate the arguments set forth in their previous response, namely that the claimed invention recites **two important features** of the TFPI and TFPI analog preparations, namely (i) commercial-grade purity (*i.e.*, less than 12% modified species) and (ii) commercial-scale quantity (*i.e.*, at least 200 grams). Applicants do not agree that the TFPI compositions disclosed in Diaz-Collier necessarily meet the recited purity level of feature (i), for reasons already of record. However, in any event, the pending claims are **even further distinguishable** over this reference because of the recited feature (ii), namely the **quantity** of the TFPI preparation or pharmaceutical formulation.

Moreover, the products of Examples I and II of Diaz-Collier do not display less than 12% modified species. Diaz-Collier analyzed the products produced by embodiments A and B of their disclosed methods at page 11, lines 3 – page 12 line 3 therein. Under the polyacrylamide gel analysis set forth on page 11, lines 37-40, Diaz-Collier states:. :

> The primary band of TFPI from both processes was identical on reduced and native gels. However on native gels the TFPI from the EXAMPLE I process had a higher content of dimer species, whereas the TFPI produced from the EXAMPLE II process had a higher content of lower molecular weight (C-terminally truncated) species. See FIG. 9.

Referring to Figure 9 of Diaz-Collier, one sees the following polyacrylamide gel, said gel providing native and denatured samples of product from embodiment A (the process of Example I) and embodiment B (the process of Example II):

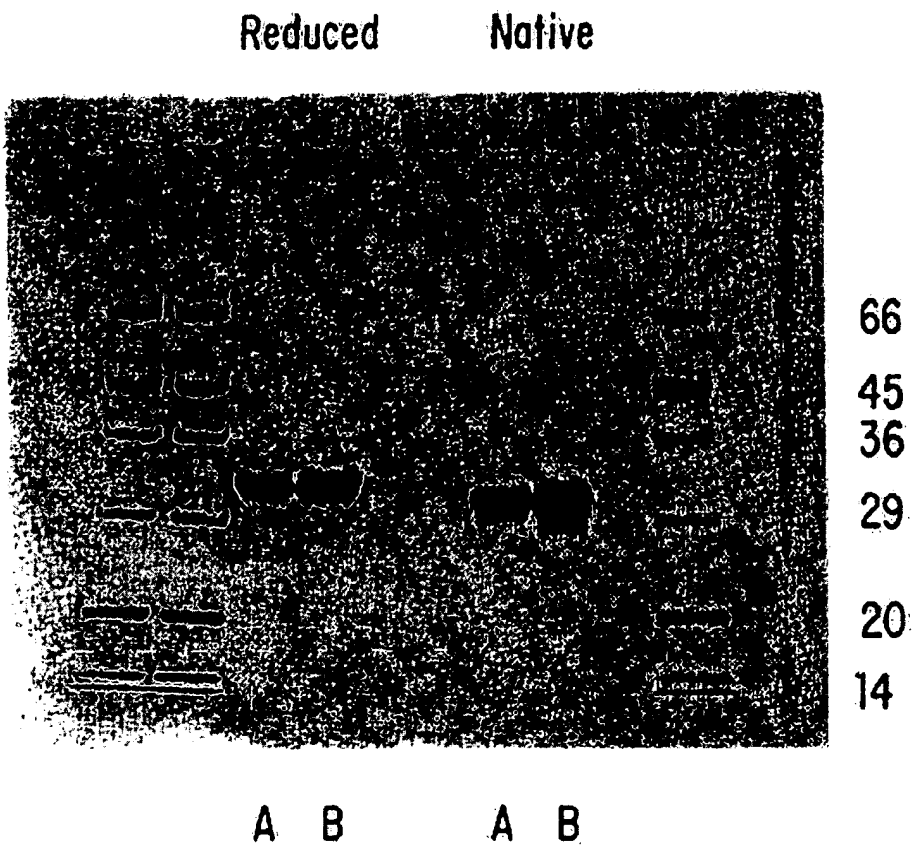

FIG. 9

It is quite noticeable that embodiment B produced by Example II, as discussed at page 11, lines 37-40, has a high content of truncated TFPI migrating at 20-25 kDa. This is noticeable in both the reduced and native lanes of the gel.[1] Moreover, embodiment A produced by Example I, and as discussed at page 11, lines 37-40, has a large content of dimer species, said dimer species being noticeable in the native lane of embodiment A (migrating at about 66 kilodaltons).

[1] Applicants note that the Office cites Example I of Diaz-Collier (embodiment A), but not Example II (embodiment B). Applicants note, as the Office has noted, that embodiment B suffers from a variety of problems, including truncation and a significant degree of heterogeneity, as show throughout the assay methods on pp. 11-12 of Diaz-Collier.

While Diaz-Collier does not assign a value to the dimer content of embodiment A, from the gel presented in Figure 9, the dimer content appears to be above 12%.[2]

Diaz-Collier uses Electrospray Mass Spectral Analysis to analyze "the mass of the primary component of TFPI produced by both processes" and determined that the primary component of TFPI produced in each sample is the same. (Page 11, line 57) Given the gel shown in Figure 9, the Mass Spectral Analysis confirms that the primary component of each sample is the TFPI monomer running at about 33 kDa. Diaz-Collier also indicates on page 12 that the material produced from Example II contained up to "30% heterogeneous species", but that the material produced from Example I was "essentially homogeneous (>95%)". (Page 11, line 57-page 12, line3). As Diaz-Collier was analyzing the TFPI species in the material produced in the examples, here Diaz-Collier is likely referring to the state of modification of the TFPI components in the samples. Thus, the material of Example I, while significantly dimerized according to Figure 9, has less than 5% modified species. Accordingly, the Diaz-Collier material of both Example I and II is excluded from the scope of Applicants claims, which require less than 12 % modified species, which can be, e.g., less than 12 % aggregated TFPI.[3]

Finally, the instantly pending claims are directed to a purified, large-scale preparation comprising at least 200 grams of tissue factor pathway inhibitor (TFPI) or TFPI analog with particular features, i.e., having less than 12% of the TFPI or TFPI analog molecules modified by one or more of: oxidiation, carbamylation, deamidation, cysteine adducts, aggregation, and misfolding. Diaz Collier provides absolutely no indication what modification(s) causes the

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[3] Even if the aggregated amount on the gel of Figure 9 is not greater than 12%, Diaz-Collier indicates that the material of Example I has ~5% other modifications. Thus, as long as the aggregation in the gel of Figure 9 is over 7% (which it appears to be), this total of 12 % (aggregated + other modifications) is outside the claim scope (assuming, of course, that such modifications correspond to those modifications listed in Applicants claims).

heterogeneity in the preparations of Example I or II. As Mass Spectrometry is used to analyze covalent bonds, the heterogeneity seen by Diaz-Collier may be, e.g., phosphorylation (not recited in the claims), acylation (not recited in the claims), alkylation (not recited in the claims), formylation (not recited in the claims), hydroxylation (not recited in the claims), racemization (not listed in the claims), sulfonation (not listed in the claims), citrullination (not listed in the claims), and/or eliminyation (not listed in the claims). The Mass Spectral results cannot be said to provide any degree of certainty what percentage (if any) of heterogeneity in the samples of Diaz-Collier arise from oxidiation, carbamylation, deamidation, cysteine adducts, aggregation, or misfolding – the only modifications relevant to the patentability of the instantly pending claims .

The Office is basing this rejection on the doctrine of inherent anticipation. Regarding inherency, MPEP 2112 states:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)

Applicants respectfully submit that the Office has not carried the initial burden of establishing a basis in fact or technical reasoning to reasonably support the determination that the allegedly inherent characteristics of Applicants' claimed preparation necessarily flow from the teachings of Diaz-Collier. (See MPEP 1221 at IV, discussing the Office's burden to establish

prima facie inherent anticipation). Indeed, as discussed above, a careful analysis of Diaz-Collier evidences that the preparations therein likely do not contain less than 12% aggregation. Moreover, there is no teaching in Diaz-Collier regarding what modification(s) cause the heterogeneity in the Mass Spectral results. Because a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference," the absence of evidence that Diaz-Collier provides the features of Applicants' claimed preparations is fatal to the Office's case of anticipation. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The preparations and pharmaceutical formulations recited in claims 1-18 and 50-56 are therefore patentable over Diaz-Collier, whether cited under 35 U.S.C. § 102 or 35 U.S.C. § 103 of the Patent Statute. Please withdraw the rejection under 35 U.S.C. § 102(b).

The Rejection of Claim 19 under 35 U.S.C. § 103

Claims 10-19, 56 and 57 are rejected as obvious over Diaz-Collier in view of Chen *et al.*, U.S. Patent No. 6,525,102 ("Chen"). Applicants respectfully traverse these rejections.

A *prima facie* case of obviousness requires that the combined teachings of the prior art references teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974) (emphasis added). Diaz-Collier and Chen do not meet this standard, because combining the teachings of these references would not result in the claimed, large-scale pharmaceutical formulations. For the reasons given above, Diaz-Collier does not disclose Applicants claimed preparations, either explicitly or inherently. Chen does not remedy this deficiency of the primary reference, Diaz-Collier, in arriving at the pharmaceutical formulations of claims 10-19, 56 and 57.

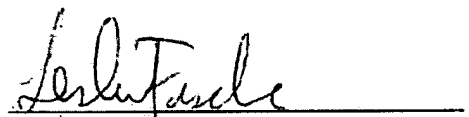
Please withdraw this rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns and rejections have been answered and overcome, and that the subject matter of the presently claimed invention satisfies the requirements of 35 USC § 112 and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims are earnestly solicited.

Applicants' undersigned attorney may be reached in our New Jersey office by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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